

Docket No. 10457-018
Application Serial No. 09/780,041

FIG. 3, panels 3A to 3F 3K, show the expression of somatically introduced transgenic tau. FIGS. 3A and 3B show the hippocampus region, with filamentous structures characteristic of this protein in neurons also being evident. The animals from which tissue was examined for FIGS. 3A and 3B received multiple genes as follows: APP, PS1, II.6 and Tau, (the behavioral modifications induced in these animals, as compared to controls, is shown in FIG. 5). Examples were found of an extracellular tau-immunoreactive deposit, about the size of a neuronal soma, in the toroidal shape reminiscent of the "ghost tangle" of Alzheimer's disease. This figure further shows that human tau gene transfer (single gene) through injection of the human four microtubule binding domain repeat P30 1L tau vector (1×10^{10} particles in 2 μ l injected 3 months earlier) led to robust expression of human tau in septal neurons of the basal forebrain. FIG. 3C shows low-magnification of the injected area, near the midline in the septal nucleus and diagonal band. Tau immunoreactivity was produced along the injection, mainly on the left side of FIG. 3C. The right edge of FIG. 3C shows surrounding, non-transduced tissue. The monoclonal antibody was specific for human tau and did not produce endogenous staining in the rat tissue. FIG. 3C shows robust levels of neurons expressing tau in the septum and diagonal band at low magnification. There is a lack of staining in the non-transduced tissue (the right edge of FIG. 3C). FIG. 3D is a confocal micrograph showing higher magnification of a neuron stained with the tau antibody where immunoreactive filaments with morphology reminiscent of flame-shaped neurofibrillary tangles are observed. This figure demonstrates that somatic gene transfer can increase tau expression and damage neurons in a manner seen in a variety of neurological disorders which encompass pathological deposits of tau, such as Alzheimer's disease, fronto-temporal dementia with Parkinsonism linked to chromosome 17, amyotrophic lateral sclerosis, Down's syndrome, Hallervorden-Spatz disease, Jakob-Creutzfeldt disease, multiple system atrophy, Pick's disease, and others. FIG. 3D shows higher magnification of the transduced cells showing somatodendritic accumulation of tau immunostaining that resemble flame-shaped neurofibrillary tangles. Higher magnification of tau accumulation in a medial septal neuron is seen in the FIG. 3D inset. FIG. 3 further shows the expression of P301L tau, and that expression resulted in tau aggregation in neuronal cell bodies and dendrites of the adult rat basal forebrain. FIGS. 3E and 3F show confocal imaging of fluorescently

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labeled tau (red) and bicistronic GFP native fluorescence, 2 months after tau vector gene transfer into the septum. Tau expression was somatodendritic as well as axonal, and punctate in places. FIGS. 3G and 3H show that at 6 months after gene transfer, a polyclonal antibody against neurofibrillary tangles labeled cell bodies in a pattern similar to the tau immunoreactivity. FIGS. 3I, 3J, and 3K show that at 6 months after gene transfer, a monoclonal antibody against paired helical filament tau labeled apparent neuritic tauopathy in the basal forebrain. This antibody recognizes the epitope containing phosphorylated serine 212 and phosphorylated threonine.

Replace the paragraph on page 17, lines 22-31 with the following:

Furthermore, FIGS. 3E 3K show the expression of P301L tau, and that expression resulted in tau aggregation in neuronal cell bodies and dendrites of the adult rat basal forebrain. (E, F) Confocal imaging of fluorescently labeled tau (red) and bicistronic GFP native fluorescence, 2 months after tau vector gene transfer into the septum. Tau expression was somatodendritic as well as axonal, and punctate in places. (G, H) At 6 months after gene transfer, a polyclonal antibody against neurofibrillary tangles labelled cell bodies in a pattern similar to the tau immunoreactivity. (I-K) At 6 months after gene transfer, a monoclonal antibody against paired helical filament tau labeled apparent neuritic tauopathy in the basal forebrain. This antibody recognizes the epitope containing phosphorylated serine 212 and phosphorylated threonine.

In the Claims:

1. (cancelled)
2. (cancelled)
3. (cancelled)
4. (cancelled)
5. (cancelled)